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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/700,491

11/05/2003

Ali Amara

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EXAMINER

CHEN, STACY BROWN

ART UNIT

PAPER NUMBER

1648

DATE MAILED: 06/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/700,491	Applicant(s) AMARA ET AL.	
	Examiner Stacy B. Chen	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-34 and 72-103 is/are pending in the application.
- 4a) Of the above claim(s) 31,72-77,86,90-95 and 101-103 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23-30,32-34,78-85,87-89 and 96-100 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>12/22/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 21, 2006 has been entered. Claims 23-34 and 72-103 are pending. Claims 23-30, 32-34, 78-85, 87-89 and 96-100 are under examination. Claims 31, 86, 72-77, 90-95 and 101-103 are withdrawn from consideration, being drawn to non-elected inventions.

2. The rejection of claims 23-30, 32-34, 78-85, 87-89 and 96-100 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a *Flaviviridae* virus infection, does not reasonably provide enablement for treatment wherein the inhibition of binding between the *Flaviviridae* virus and the effector molecule is greater than 80%, is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 112

3. (*New Rejection*) Claims 23-30, 32-34, 78-85, 87-89 and 96-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The claims are drawn to a method of treating a Flaviviridae virus infection of a mammal comprising, administering to the mammal a molecule that binds to the DC-SIGN receptor. The identity of the DC-SIGN receptor is not clear. According to the specification,

- DC-SIGN is the ligand of ICAM-3, which enables transient DC-T cell interactions, thus facilitating primary immune response [013]. DC-SIGN is expressed on dendritic cells and ICAM-3 is expressed on T-cells. According to this definition, the claimed method involves administering a molecule that binds ICAM-3.
- DC-SIGN and DC-SIGN receptor are synonymous terms [055]. The acronym, “DC-SIGN” does not include the term “receptor”. It is unclear how a ligand (DC-SIGN) and its receptor (DC-SIGN receptor) can be one and the same. Clarification is required.

Based on these two definitions, the metes and bounds of the term, “DC-SIGN receptor” cannot be determined. The methods of treating also take on a different meaning when viewed in light of these two definitions. Either the method involves administering a molecule that binds to ICAM-3, or the molecule binds to the DC-SIGN (or DC-SIGN receptor?) on the dendritic cell, thus blocking virus binding and entry.

4. (*New Rejection*) Claims 23-30, 32-34, 78-85, 87-89 and 96-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a method of treating a Flaviviridae virus

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infection of a mammal comprising, administering to the mammal a molecule that binds to the DC-SIGN receptor. The identity of the DC-SIGN receptor is not clear (see above).

If the method of treatment encompasses administering to a mammal a molecule that binds to the mammal's ICAM-3 (a DC-SIGN receptor), then the specification is completely non-enabled. Applicant has failed to explain how binding ICAM-3 would inhibit binding between DC-SIGN and Dengue, for example.

If the method of treatment encompasses administering to a mammal a molecule that binds to the mammal's DC-SIGN expressed on their dendritic cells, then the method claims are non-enabled for their asserted ability to treat a *Flaviviridae* virus infection *in vivo*. The Office recognizes that methods of treatment were previously indicated as enabled by the specification. However, upon further consideration of the state of the art and Applicant's disclosure, methods of treatment are not adequately enabled by the specification such that one of skill in the art would be equipped to practice the claimed methods.

The breadth of the claims is unreasonable, encompassing the inhibition of binding between the *Flaviviridae* virus and the mammal's dendritic cells, in a mammal already infected with the virus. The family of flaviviruses includes for example, Hepatitis C (HCV), Yellow fever, Dengue, Japanese encephalitis, tick-borne encephalitis, pestivirus, border disease and classical swine fever virus.

The nature of the invention is the inhibition of any of these viruses of the flavivirus family by blocking entry of these viruses into dendritic cells by preventing a viral molecule (such as envelope) from binding DC-SIGN.

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The state of the art surrounding DC-SIGN and flavivirus infection is that *in vivo* experiments have demonstrated a relationship between DC-SIGN and flavivirus envelope protein. Navarro-Sanchez *et al.* (*EMBO reports*, 2003, 4(7):723-728) discloses that DC-SIGN is essential for the productive infection of human dendritic cells by mosquito-cell-derived dengue viruses. Navarro-Sanchez *et al.* demonstrated this by inhibiting viral infection by anti-DC-SIGN antibodies and by the soluble tetrameric ectodomain of DC-SIGN (abstract). Navarro-Sanchez *et al.* discloses that the relevance of this discovery remains to be tested *in vivo*.

The level of skill in the art is high, evidenced by those of skill in the prior art.

The level of predictability in the art is low because the mechanism described in this invention is novel, and thus *in vivo* experimentation is required to determine whether *in vitro* results reflect *in vivo* performance. As outlined previously, the Centers for Disease Control (CDC) reports that there is no vaccine for Dengue virus and that efficacy trials in humans have yet to be initiated as of the year 2003 (see website printout, page 4, "Future Outlook" section). Leyssen *et al.* (*Clin. Microbiol. Rev.* 2000, 13(1):67-82, herein, "Leyssen") confirms that there are no vaccines or treatments for Dengue virus (page 72, column 1, first full paragraph). Current treatment for HCV is ribavirin, but with limited results and no protection (Leyssen, page 72, top incomplete paragraph). Leyssen teaches that little is known about flavivirus entry and cell receptor (page 73, columns 1 and 2, bridging paragraph). Leyssen also discloses that because of "the genetic and serological heterogeneity of HCV, the development of effective vaccines will be difficult and is not expected to occur soon" (page 76, column 2, last paragraph). Regarding Dengue virus, Japanese encephalitis virus and tick-borne encephalitis virus, Leyssen discloses

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that there are no drugs yet available (page 76, column 2, last paragraph). Men *et al.* (*J. Virology*, 2004, 78(9):4665-4674) also confirms that there are no vaccines for Dengue virus (abstract).

The specification does not provide guidance for inhibiting virus entry *in vivo*. If one of skill in the art were to treat a flavivirus infection, given the claimed methods and specification, one would not know what dosage of antibody, for example, should be used for binding DC-SIGN. Given the abundance of dendritic cells in an individual, one would have to consider what dosage of antibody would be appropriate for binding a significant number of dendritic cells such that the virus (already present in the body) would be inhibited. Applicant has not taught what effective amount of antibodies would result in a therapeutic benefit for the patient (an improvement in a symptom). Given the fast-acting viral pathology of Dengue virus, one would need to know the effective amount and frequency that would inhibit the binding of virus to dendritic cells.

The working examples include *in vitro* binding inhibition of *Flaviviridae* virus. While this data is useful for demonstrating that there is relationship between DC-SIGN and flaviviruses, the data cannot be extrapolated to methods of improving the symptoms of any and all mammals infected with a flavivirus.

Given the breadth of the claims, the nature of the invention, the state of the prior art, the level of skill in the art, the low level of predictability, the lack of guidance and working examples, it would require undue experimentation to use the claimed invention as claimed. Further experimentation is required before *in vivo* applications are adequately enabled. Given this new mechanism of virus inhibition, one of skill cannot predict the *in vivo* results with any degree of certainty. Therefore, the claims are not enabled by the specification.

Conclusion

5. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 6/5/06

Stacy B. Chen
Primary Examiner
June 5, 2006